

WHAT IS CLAIMED IS:

1. An elastase-resistant ATIII, comprising an ATIII comprising a compound of Formula I at residues 389 and 390:

D-E

Formula I

wherein D is selected from the group consisting of: glutamic acid; phenylalanine; glycine; and proline; and

E is selected from the group consisting of: alanine; phenylalanine; glycine; and proline;

or a pharmaceutically-acceptable formulation thereof.

2. An elastase-resistant ATIII of claim 1, which further comprises a compound selected from the group of: Formula II at residues 386-388; and Formula III at residue 391,

A-B-C

Formula II

wherein A is selected from the group consisting of: threonine; and glutamic acid, and

wherein B is selected from the group consisting of: alanine; glutamic acid; and glutamine, and

wherein C is selected from the group consisting of: leucine; valine; glycine; glutamic acid and threonine, and

F

Formula III

wherein F is selected from the group consisting of: alanine; isoleucine; serine; glycine; and asparagine.

FOOTNOTES

3. An elastase-resistant ATIII of claim 2, wherein said ATIII has enhanced heparin affinity.
4. An elastase-resistant ATIII of claim 3, wherein said ATIII has enhanced heparin affinity by virtue of a mutation two residues subsequent to a glycosylation site.
5. An elastase-resistant ATIII of claim 2, wherein D is glutamic acid and E is alanine.
6. An elastase-resistant ATIII of claim 5, wherein A is threonine, B is glutamic acid, C is glycine and F is serine.
7. An elastase-resistant ATIII of claim 5, wherein A is threonine, B is glutamic acid, C is valine and F is alanine.
8. An elastase-resistant ATIII of claim 5, wherein A is threonine, B is alanine, C is leucine and F is isoleucine.
9. An elastase-resistant ATIII of claim 2, wherein D is glutamic acid and E is glycine.
10. An elastase-resistant ATIII of claim 9, wherein A is threonine, B is glutamic acid, C is leucine and F is alanine.
11. An elastase-resistant ATIII of claim 2, wherein D is phenylalanine and E is phenylalanine.
12. An elastase-resistant ATIII of claim 11, wherein A is threonine, B is glutamic acid, C is glycine and F is serine.
13. An elastase-resistant ATIII comprising an amino acid sequence at residues 386 through 391 selected from the group consisting of: SEQ ID NO 1; SEQ ID NO 2; SEQ ID NO 3; SEQ ID NO 4; SEQ ID NO 5; SEQ ID NO 6; SEQ ID NO 7; SEQ ID NO 8; SEQ ID NO 9; SEQ ID NO 10; SEQ ID NO 11; SEQ ID NO 12; SEQ ID NO 13; and SEQ ID NO 14; and SEQ ID NO 15, or a pharmaceutically-acceptable formulation thereof.
14. A nucleic acid molecule comprising a nucleic acid molecule which encodes a compound of claim 1.

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15. A nucleic acid molecule encoding an elastase-resistant ATIII amino acid molecule of claim 13.
16. A method to inhibit thrombin activation, comprising administering a compound of claim 1.
17. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 1.
18. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 2.
19. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 3.
20. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 4.
21. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 5.
22. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 8.
23. A method to inhibit thrombin activation in a patient in need of such inhibition, comprising administering a compound of claim 12.
24. A method to inhibit factor Xa, comprising administering a compound of claim 1.
25. A method of to inhibit factor Xa in a patient in need of such inhibition, comprising administering a compound of claim 1, except that when A is glutamic acid, E is alanine.
26. A method to inhibit thrombin in a patient in need of such inhibition, comprising administering a compound of claim 8.
27. A method to inhibit thrombin in a patient in need of such inhibition, comprising administering a compound of claim 12.

28. A method to treat a thrombin activation-related pathological symptom in a patient in need of such treatment, comprising administering a compound of claim 1.
29. A method of claim 28, wherein the pathological symptom is due to a pathology selected from the group consisting of: sepsis; trauma; acute respiratory distress syndrome; reocclusion with restenosis; thrombosis; thromboembolism; stroke; and restenosis.
30. A method to reduce the risk of a thrombin activation-related pathological symptom in a patient in need of such treatment, comprising administering a compound of claim 1.
31. A method of claim 30, wherein the thrombin activation-related pathological symptom for which the risk is reduced is selected from the group consisting of: reocclusion and restenosis in percutaneous transluminal coronary angioplasty; thrombosis associated with surgery; ischemia/reperfusion injury; and coagulation abnormalities in cancer or surgical patients.
32. A method of claim 31, wherein the coagulation abnormalities associated with surgical patients are those associated with cardiopulmonary bypass.
33. A method to reduce the risk of thrombosis in a patient in need of such reduction, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
34. A method to reduce the risk of restenosis in a patient in need of such reduction, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
35. A method to reduce the risk of reocclusion in a patient in need of such reduction, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
36. A method to reduce the risk of coagulation abnormalities in a patient in need of such reduction, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.

37. A method of claim 36, wherein the risk of coagulation abnormalities is associated with cardiopulmonary bypass.
38. A method to treat sepsis in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 1; and a nucleic acid which encodes a compound of claim 1.
39. A method to treat sepsis in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
40. A method to treat trauma in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
41. A method to treat acute respiratory distress syndrome in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
42. A method to treat ischemic stroke in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
43. A method to treat thrombosis in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
44. A method to treat restenosis in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.
45. A method to treat reocclusion in a patient in need of such treatment, comprising administering a compound selected from the group consisting of: a compound of claim 13; and a nucleic acid which encodes a compound of claim 13.

46. A method for producing human antithrombin III in bodily fluid, comprising: producing a transgenic animal that expresses in bodily fluid a transgene which encodes an elastase-resistant ATIII of claim 1, wherein the human antithrombin III is secreted into the bodily fluid produced by the transgenic animal; collecting bodily fluid from the transgenic animal, which bodily fluid contains the human antithrombin III; and isolating the human antithrombin III from the collected bodily fluid.
47. A method of claim 46, wherein the bodily fluid is selected from the group consisting of: milk or urine.
48. A method of claim 46, wherein the bodily fluid is milk, and the animal is selected from the group consisting of: goat; sheep; and cow.
49. A method for producing human antithrombin III in goat milk, comprising: producing a transgenic goat that expresses in mammary tissue a transgene which encodes an elastase-resistant ATIII of claim 1, wherein the human antithrombin III is secreted into the milk produced by the transgenic goat; collecting milk from the transgenic goat which milk contains the human antithrombin III; and isolating the human antithrombin III from the collected milk.